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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,440	10/14/2003	Donald E. Ackley	612,404-430	6873

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EXAMINER	
BOWERS, NATHAN ANDREW	
ART UNIT	**PAPER NUMBER**
1744	

DATE MAILED: 12/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/686,440	ACKLEY ET AL.	
	Examiner	Art Unit	
	Nathan A. Bowers	1744	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1) Claims 1, 4, 5, 6, 7, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chow (US 6494230 B2) in view of Anderson (US 5922591).

With respect to claims 1, 4, 5, and 6, Chow discloses a method and device comprising an inlet (Figure 1:126, 130) for receipt of a sample, a first chamber (Figure 1:122) coupled to the inlet, and a second chamber (Figure 1:124) stacked on top of the first chamber. An outlet (Figure 1:132) is coupled to the second chamber. Chow teaches in column 2, lines 12-44 and column 6, line 44 to column 7, line 22 that the first and second chambers are in fluid communication through a network of channels. Column 7, line 53 to column 8, lines 18 disclose a variety of pumping systems regulating the direction of fluid flow. This indicates that Chow's invention is inherently capable of moving fluids inserted in the first chamber upwards into the second chamber, and then through outlets directed from the top of the second chamber. The second chamber comprises a top member (Figure 1:106) and a second spacer, and the first chamber comprises a bottom support (Figure 1:102) and a first spacer. The first and second spacers are formed from the top lips of the substrates upon which the chambers etched. The first and second chambers share a common intermediate member (Figure

1:104) that has at least via formed therein. Chow teaches in column 14, lines 5-10 that the chambers may be used for a variety of biochemical applications, including nucleic acid analysis and genetic testing and identification. Therefore, Chow's invention intrinsically must comprise at least one affinity region in the first and second chambers. Chow, however, does not expressly state that the second chamber includes an assay chip comprising an array of addressable electrodes.

Anderson discloses a microfluidic device comprising a series of reaction chambers (Figure 3:202, 206, 210, 214, 218). The chambers are connected in series by channels (Figure 3:204, 208, 212, 216) so that adjacent chambers each have peripheral boundary defined by common intermediate member. This construction is described in column 22, lines 44-54. Column 5, line 59 to column 6, line 9 and column 20, lines 59-65 teach that inlets and outlets are provided at each chamber, and that means are provided for introducing and expelling sample to and from the overall device. Anderson teaches in column 35, lines 57-65 that a multitude of electrodes may be incorporated onto the hybridization arrays of the analysis chamber. This would allow an operator one to skip any fluorescent or radioactive labeling step, since the presence of nucleic acids bound to the probes can be detected electrically. In light of this teaching, it is possible for DNA amplified in a first chamber to move directly to a second chamber comprising an array of electrodes that facilitate hybridization and detection.

Chow and Anderson are analogous art because they are from the same field of endeavor regarding the manipulation and analysis of nucleic acids within a fluid sample.

At the time of the invention, it would have been obvious to utilize Chow's stacked, multi-chambered analysis device to manipulate nucleic acid samples using a plurality of affinity, amplification, and detection regions. In column 3, lines 22-36, Chow teaches that a stacked relationship between a sequence of chambers is desirable because it permits optimal use of substrate materials, allows increased miniaturization of fluidic processes, provides substantial cost advantages, and permits the simultaneous sue of individual electrode interfaces on multiple layers. It would have further been beneficial to add an assay chip comprising an array of addressable electrodes to the second chamber in order to analyze the amplification results. Anderson teaches in column 22, line 55 to column 24, line 19 and in column 35, lines 57-65 that amplification and detection may be efficiently achieved in neighboring chambers that implement affinity regions and addressable electrode arrays. In this way, it would have been apparent to modify Chow's device in order to facilitate DNA amplification and analysis without altering the relationship between the first and second chambers.

With respect to claims 7 and 8, Chow and Anderson disclose the combination as cited above. However, Chow does not specifically disclose that nucleic acids are amplified in the first chamber and then eluted through the via into the second chamber.

Anderson discloses in column 22, line 55 to column 24, line 19 an example in which a first chamber is used for sample collection, a second chamber for purification, a third chamber for nucleic acid amplification, a forth chamber for labeling, and a fifth for probe array analysis. Anderson teaches in column 2, lines 20-30 and column 22, lines

55-57 that the device may be used for a variety of preparative and analytical operations in which individual chambers assume various functions. Therefore, it is an intrinsic feature of this invention that if a previously purified DNA sample is provided, initial isolation steps will be skipped so that DNA amplification takes place in the first chamber. Here, the DNA will selectively bind to primers and polymerase enzymes, thus constituting an affinity region. For example, in Figure 15a and in column 40, line 66 to column 41, line 37 an embodiment of the invention is detailed in which PCR proceeds in the first chamber. Once PCR is complete, the amplified nucleic acid is eluted through the channel via into the second chamber for further analysis.

At the time of the invention, it would have been obvious to alter the method proposed by Chow in order to amplify nucleic acids in the first chamber, and then elute the amplified product through the via into the second chamber. Anderson states in column 1, line 30 to column 2, line 17 that the study of genetic information is of great value because it leads to advances in a number of disciplines including chemistry, molecular biology, and medicine. Column 5, lines 32-43 state that in order for extensive research to take place, a DNA product must initially be amplified and moved to a plurality of subsequent analytical chambers. Therefore, it would have been obvious to use Chow's device to amplify nucleic acids in a first chamber and move the product to a second chamber in order to provide a device capable of fully processing a DNA sample.

2) Claims 1, 4, 5, 6, 7, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyberg (US 5788826) in view of Anderson (US 5922591).

With respect to claims 1, 4, 5, and 6, Nyberg discloses a device (Figure 1:20) comprising an inlet (Figure 1:30) for receipt of a sample, a first chamber coupled to the inlet, and a second chamber stacked on top of the first chamber. An outlet is coupled to the second chamber. This is taught in column 8, lines 7-55 and in column 5, line 55 to column 6, line 29. The second chamber comprises an electrode (Figure 1:45), a top member, and a second spacer (Figure 1:155), and the first chamber comprises an electrode (Figure 1:40), a bottom support, and a first spacer (Figure 1:25). The first and second chambers share a common intermediate member (Figure 1:100) that has at least one via formed therein. In this way, both electrodes are positioned adjacent to the via. Fluids enter the first chamber by way of the inlet, move through the via formed in the intermediate member, and exit the second chamber using the outlet. Fluid motion is indicated by arrow 121 in Figure 1. Column 10, lines 27-48 teach that the intermediate member comprises a membrane having cation exchange surfaces (Figure 1:105) and anion exchange surfaces (Figure 1:110) that act as affinity regions since they selectively remove and replace ions in the solution streams. Nyberg, however, does not expressly state that the second chamber includes an assay chip comprising an array of addressable electrodes, or that the affinity region has affinity to nucleic acids.

Anderson discloses a microfluidic device comprising a series of reaction chambers (Figure 3:202, 206, 210, 214, 218). The chambers are connected in series by channels (Figure 3:204, 208, 212, 216) so that adjacent chambers each have peripheral boundary defined by common intermediate member. This construction is described in column 22, lines 44-54. Column 5, line 59 to column 6, line 9 and column

20, lines 59-65 teach that inlets and outlets are provided at each chamber, and that means are provided for introducing and expelling sample to and from the overall device. Anderson teaches in column 35, lines 57-65 that a multitude of electrodes may be incorporated onto the hybridization arrays of the analysis chamber. This would allow an operator one to skip any fluorescent or radioactive labeling step, since the presence of nucleic acids bound to the probes can be detected electrically.

Nyberg and Anderson are analogous art because they are from the same field of endeavor regarding laboratory fluidic devices designed to carry out analysis on a sample solution.

At the time of the invention, it would have been obvious to utilize Nyberg's stacked, multi-chambered analysis device to manipulate nucleic acid samples using a plurality of affinity, amplification, and detection regions, rather than just to remove and replace ions in solution streams. Anderson teaches in column 1, line 31 to column 2, line 17 that the study of genetic sequences using microfabricated devices is of great importance, and is likely to lead to a better understanding of life processes, and the ability to diagnose and treat a large number of disorders. Therefore, it would have been desirable to equip the first chamber disclosed by Nyberg with at least one affinity region in order to promote nucleic acid amplification. It would have further been beneficial to add an assay chip comprising an array of addressable electrodes to the second chamber in order to analyze the amplification results. Anderson teaches in column 22, line 55 to column 24, line 19 and in column 35, lines 57-65 that amplification and detection may be efficiently achieved in neighboring chambers that implement affinity

regions and addressable electrode arrays. In this way, it would have been apparent to modify Nyberg's device in order to facilitate DNA amplification and analysis without altering the disclosed flow pattern and relationship between the first and second chambers.

With respect to claims 7 and 8, Nyberg and Anderson disclose the combination as cited above. However, Nyberg does not disclose that nucleic acids are amplified in the first chamber and then eluted through the via into the second chamber.

Anderson discloses in column 22, line 55 to column 24, line 19 an example in which a first chamber is used for sample collection, a second chamber for purification, a third chamber for nucleic acid amplification, a forth chamber for labeling, and a fifth for probe array analysis. Anderson teaches in column 2, lines 20-30 and column 22, lines 55-57 that the device may be used for a variety of preparative and analytical operations in which individual chambers assume various functions. Therefore, it is an intrinsic feature of this invention that if a previously purified DNA sample is provided, initial isolation steps will be skipped so that DNA amplification takes place in the first chamber. Here, the DNA will selectively bind to primers and polymerase enzymes, thus constituting an affinity region. For example, in Figure 15a and in column 40, line 66 to column 41, line 37 an embodiment of the invention is detailed in which PCR proceeds in the first chamber. Once PCR is complete, the amplified nucleic acid is eluted through the channel via into the second chamber for further analysis.

At the time of the invention, it would have been obvious to alter the method proposed by Nyberg in order to amplify nucleic acids in the first chamber, and then elute the amplified product through the via into the second chamber. Anderson states in column 1, line 30 to column 2, line 17 that the study of genetic information is of great value because it leads to advances in a number of disciplines including chemistry, molecular biology, and medicine. Column 5, lines 32-43 state that in order for extensive research to take place, a DNA product must initially be amplified and moved to a plurality of subsequent analytical chambers. Therefore, it would have been obvious to use Nyberg's device to amplify nucleic acids in a first chamber and move the product to a second chamber in order to provide a device capable of fully processing a DNA sample.

3) Claims 2, 3, 4, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chow (US 6494230 B2) in view of Anderson (US 5922591) as applied to claim 1 above, and further in view of Hollis (US 5653939).

Chow and Anderson disclose the apparatus set forth in claim 1 as set forth in the 35 U.S.C. 102 rejection above. Anderson further expresses certain design conditions which indicate that the first chamber includes an affinity region comprising a membrane fabricated to selectively retain nucleic acids. However, Chow and Anderson do not explicitly teach that the first chamber includes a plurality of electrodes.

Hollis discloses a microfluidic chamber comprising a chip with an array (Figure 1:10) of test sites (Figure 1:12). This is described in column 2, lines 30-43. Each test site contains a plurality of wells (Figure 4:42) that capture a portion of sample fluid that

is poured across the array. A plurality of electrodes (Figure 4:16, 20, 21) are distributed within each well, so that the every test site comprises a multitude of electrodes according to column 4, lines 50-53. Column 11, lines 5-34 teach that hybridization probes (Figure 4:22) are attached to each electrode, and column 7, line 64 to column 8, line 20 indicates that membranes are formed over electrodes to provide an adequate binding medium for the probes. Based on applicant's description of an affinity matrix in paragraphs [0010], [0041], and [0057] of the application, Hollis's electrode hybridization array meets the necessary criteria to be considered an affinity matrix.

Chow, Anderson, and Hollis are analogous art because they are from the same field of endeavor regarding the manipulation and analysis of nucleic acids within a fluid sample.

At the time of the invention, it would have been obvious to a person of ordinary skill in the art to implement the same array construction described by Hollis into the first chamber of Chow and Anderson's microfluidic device. In column 35, lines 57-65, Anderson states a desire to incorporate electrodes into hybridization analysis procedures that take place in various successive chambers following the first chamber. Since detection is often the ultimate goal, it would have been apparent to implement probe arrays in the first chamber as well to partially analyze the solution at the start, especially if a purified sample is already obtained. Hollis states in column 2, lines 41-52 that his electrode array is a low cost, small in size, and inexpensive, and, therefore, an attractive option for hybridization procedures. This is especially due to the fact that the electrodes not only present a safe and quick way of detecting nucleic acid binding, but

also can serve to actively draw the ligand towards the probe by producing an electrical current. Furthermore, Hollis teaches in column 11, lines 5-34 and column 8, lines 13-17 that overlaying each electrode with a membrane is desirable because membranes enhance the formation of covalent linkages between electrodes and probes, while keeping nucleic acids in solution from directly contacting the electrodes.

Response to Arguments

Applicant's arguments, see page 5, lines 6-21, filed 28 October 2005, with respect to the rejection(s) of claim(s) 1-8 under 35 USC §102(b) and 35 USC §103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Chow (US 6494230 B2) and Nyberg (US 5788826).

Applicant's principle arguments are

(a) Applicant has amended claim 1 to further clarify that the first and second chambers are stacked on top on one another. Applicant respectfully submits that Anderson does not anticipate the invention as disclosed, because Anderson discloses "a microfluidic device comprising a series of reaction chambers" wherein "the chambers are connected in series by channels."

In response to Applicant's arguments, please consider the following comments.

It should be appreciated that Chow's device and Nyberg's device comprise first and second chambers that are stacked on top of one another and separated by a common intermediate member that includes at least one via therethrough. Either Chow or Nyberg may be combined with Anderson or with Anderson and Hollis in order to meet

the limitations posed by claims 1-8. Anderson and Hollis provide sufficient reason and motivation to include various biochemical affinity, amplification, and detection regions within Nyberg's device, as well as the necessary motivation to expand the nucleic acid analysis capabilities of Chow's device. These include, but are not restricted to, an affinity matrix to facilitate PCR in the first chamber, and an array of addressable electrode to promote detection and analysis in the second chamber.

Therefore, all 35 USC §103(a) rejections that are made with Chow or Nyberg serving as the principle prior art and including Anderson and Hollis are pertinent to the instant application.

Terminal Disclaimer

The terminal disclaimer filed on 24 October 2005 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent Nos. 6,309,602, 6,319,472, 6,638,482, and 6,375899 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this office action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan A. Bowers whose telephone number is (571)272-8613. The examiner can normally be reached on Monday-Friday 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sun (John) Kim, Ph.D. can be reached on (571)272-1142. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NAB

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